

PENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT**NOTIFICATION OF THE RECORDING
OF A CHANGE**(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)Date of mailing 01 May 1996
(day/month/year) (01.05.96)

To:

RAE, Patricia, A.
Sim & McBurney
701 - 330 University Avenue
Toronto, Ontario M5G 1R7
CANADAApplicant's or agent's file reference
4767-49/PAR**IMPORTANT NOTIFICATION**International application No.
PCT/CA95/00287International filing date 12 May 1995
(day/month/year) (12.05.95)

1. The following indications appeared on record concerning:

 the applicant the inventor the agent the common representative

Name and Address LONDON HEALTH ASSOCIATION P.O. Box 5339 London, Ontario N6A 5A5 Canada	State of Nationality CA	State of Residence CA
Telephone No.		
Facsimile No.		
Teleprinter No.		

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

 the person the name the address the nationality the residence

Name and Address VICTORIA/UNIVERSITY HOSPITAL CORPORATION 800 Commissioners Road East London, Ontario N6A 4G5 Canada	State of Nationality CA	State of Residence CA
Telephone No.		
Facsimile No.		
Teleprinter No.		

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer M. Lee Telephone No. (41-22) 730.91.11
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PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing (day/month/year) 22 December 1995 (22.12.95)	
International application No. PCT/CA95/00287	Applicant's or agent's file reference 4767-49/PAR
International filing date (day/month/year) 12 May 1995 (12.05.95)	Priority date (day/month/year) 12 May 1994 (12.05.94)
Applicant DUPRE, John	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

04 December 1995 (04.12.95)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Martine Lee Telephone No.: (41-22) 730.91.11
---	---

PATENT COOPERATION TREATY

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PCT

JUL 8 1996

SIM & MCBURNEY
SIM, HUGHES, ASHTON & MCKAYFrom the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

RAE, Patricia A.
Sim & McBurney
330 University Avenue
Suite 701
Toronto, Ontario M5G 1R7
CANADA

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

25. Juni 1996

Applicant's or agent's file reference
4767-49/PAR

IMPORTANT NOTIFICATION

International application No.
PCT/CA 95/00287International filing date (day/month/year)
12/05/1995Priority date (day/month/year)
12/05/1994

Applicant

VICTORIA/UNIVERSITY HOSPITAL CORP. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

Telephone No.

J. Lausenmeyer

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4767-49/PAR	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/ CA 95/ 00287	International filing date (day/month/year) 12/05/1995	Priority date (day/month/year) 12/05/1994	
International Patent Classification (IPC) or national classification and IPC A61K38/26			
Applicant VICTORIA/UNIVERSITY HOSPITAL CORP. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

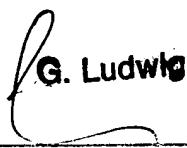
2. This REPORT consists of a total of **5** sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of **1** sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 04/12/1995	Date of completion of this report 25. Juni 1996
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  G. Ludwig Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/CA95/00287

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

the international application as originally filed.

the description, pages 1-11 _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

the claims, Nos. 1-5, 6(part), 13(part)-14 _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 6(part), 7-12, 13(part), filed with the letter of 10.5.96,
Nos. _____, filed with the letter of _____,

the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

the description, pages _____.
 the claims, Nos. _____.
 the drawings, sheets/fig _____.

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-9, 11-14 _____	YES
	Claims 10 _____	NO
Inventive Step (IS)	Claims 4, 8, 11, 13-14 _____	YES
	Claims 1-3, 5-7, 9-10, 12 _____	NO
Industrial Applicability (IA)	Claims 1-14 - cf. text _____	YES
	Claims _____	NO

2. CITATIONS AND EXPLANATIONS

1. The following documents (D) are referred to in this report:

D1: WO 91/11457
D2: The New England Journal of Medicine 326, 1316-1322
(1992)
D3: The Journal of Clinical Investigation 93, 2263-2266
(1994)

2. According to the WHO-classification insulin-dependent diabetes mellitus (IDDM) is called type I diabetes. IDDM patients have a dependence on insulin to prevent life threatening ketosis.

This is normally not the case in patients with non-insulin requiring diabetes (NIDDM) which is called type II diabetes.

Of diagnosed diabetes about 55% appears to be NIDDM not treated with insulin and about 30% is NIDDM treated with insulin.

2.1 "Insulin-requiring diabetes" as used in the claims of the specification can be understood to refer to all diabetics which are unable to avoid hyperglycemia without the use of insulin.

This term therefore encompasses both type I (IDDM) and type II (NIDDM) diabetes.

3. Document D1 discloses the use of glucagon-like peptide 1 (7-36 or 7-37) [GLP-1 or GLIP] or amides thereof for the treatment of type II diabetes.

Document D2 discloses that GLIP (amide) may be useful in the treatment of type II diabetes (NIDDM).

Document D2 states that a better treatment for patients with NIDDM who do not respond to sulfonylurea therapy would be one that decreased their requirement for insulin and therefore decreased the occurrence of hyperinsulinemia. The study of D2 demonstrates that at least in the short term, the administration of GLIP decreases postpranial insulin requirements and plasma insulin concentrations in patients with NIDDM. Therefore this peptide may have a role in the treatment of some patients with diabetes.

Although document D2 shows, *inter alia*, that in patients with IDDM infusion of GLIP decreased the calculated isoglycemic meal-related insulin requirement a potential use of GLIP for the treatment of IDDM (type I diabetes) patients is not indicated in this study.

Document D3 discloses that GLIP (amide) increases glucose effectiveness (relevant for type II diabetes) and that it also increases insulin secretion (relevant for type I diabetes). However, the cautious conclusions of the authors of the end of this basic biochemical/pharmacological study do not appear to suggest the use of GLIP for the treatment of diabetes type I or type II.

4. In view of the above it appears that the state of the art does not suggest a treatment of type I diabetes (IDDM) by GLIP.

Claims 4, 8, 11 and 13-14 are therefore considered as novel and inventive.

5. It appears that the skilled man, starting from document D1 and having regard to documents D2-D3, wanting to provide a further (improved) treatment of NIDDM (type II diabetes) would want to use GLIP, alone or in combination with insulin for the treatment of this disease.

Claims 1, 5-6 and 9-10 are therefore not inventive. Accordingly, this also holds for the dependent claims 2-3, 7 and 12.

6. For the assessment of the presently worded claims 1-5 and 13 on the question whether it is industrially applicable, no unified criteria exist in the PCT. In the Contracting States of the PCT the patentability of such a claim can also depend on its formulation. Accordingly, the applicant is informed that under the EPC these claims would not be allowable (Art. 52(4) & 52(1) EPC).

regimen which additionally comprises treatment with insulin.

7. Use of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) for the preparation of a medicament which also includes insulin for treatment of insulin-requiring diabetes.

8. Use of a peptide in accordance with claim 6 or 7 wherein the insulin-requiring diabetes is Type I diabetes.

9. Use of a peptide in accordance with claim 6 or 7 wherein the insulin-requiring diabetes is Type II diabetes.

10. A pharmaceutical composition for the treatment of insulin-requiring diabetes comprising an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition in accordance with claim 10 for the treatment of Type I diabetes.

12. The pharmaceutical composition of claim 10 or 11 further comprising an effective amount of insulin.

13. A method of treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
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CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Malta	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

regimen which additionally comprises treatment with insulin.

7. Use of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b)

for the preparation of a medicament which also includes insulin for treatment of insulin-requiring diabetes.

8. Use of a peptide in accordance with claim 6 wherein the insulin-requiring diabetes is Type I diabetes.

9. Use of a peptide in accordance with claim 7 wherein the insulin-requiring diabetes is Type I diabetes.

10. A pharmaceutical composition for the treatment of insulin-requiring diabetes comprising an effective amount of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b)

and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition in accordance with claim 10 for the treatment of Type I diabetes.

12. The pharmaceutical composition of claim 10 or 11 further comprising an effective amount of insulin.

13. A method of treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);

Replaced by Article 34

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 4767-49/PAR

Box No. I TITLE OF INVENTION

TREATMENT OF DIABETES

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LONDON HEALTH ASSOCIATION (Owner and Operator of University Hospital)

P.O. Box 5339
London, Ontario
N6A 5A5 Canada

This person is also inventor.

Telephone No.
(519) 663-3300

Faximile No.
(519) 663-3232

Teleprinter No.

State (i.e. country) of nationality:

CA

State (i.e. country) of residence:

CA

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

DUPRE, John
72 Sherwood Avenue
London, Ontario
N6A 2E2 Canada

This person is:

applicant only

applicant and inventor

inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

CA

State (i.e. country) of residence:

CA

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

agent

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

RAE, Patricia A.
Sim & McBurney
701 - 330 University Avenue
Toronto, Ontario
M5G 1R7 Canada

Telephone No.

(416) 595-1155

Faximile No.

(416) 595-1163

Teleprinter No.

Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

AP ARIPO Patent: KE Kenya, MW Malawi, SD Sudan, SZ Swaziland and any other State which is a Contracting State of the Harare Protocol and of the PCT

EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

AM Armenia

AT Austria

AU Australia

BB Barbados

BG Bulgaria

BR Brazil

BY Belarus

CA Canada

CH and LI Switzerland and Liechtenstein

CN China

CZ Czech Republic

DE Germany

DK Denmark

EE Estonia

ES Spain

FI Finland

GB United Kingdom

GE Georgia

HU Hungary

JP Japan

KE Kenya

KG Kyrgyzstan

KP Democratic People's Republic of Korea

KR Republic of Korea

KZ Kazakhstan

LK Sri Lanka

LR Liberia

LT Lithuania

LU Luxembourg

LV Latvia

MD Republic of Moldova

MG Madagascar

MN Mongolia

MW Malawi

MX Mexico

NL Netherlands

NO Norway

NZ New Zealand

PL Poland

PT Portugal

RO Romania

RU Russian Federation

SD Sudan

SE Sweden

SI Slovenia

SK Slovakia

TJ Tajikistan

TT Trinidad and Tobago

UA Ukraine

US United States of America

UZ Uzbekistan

VN Viet Nam

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

IS Iceland

UG Uganda

SG Singapore

TM Turkmenistan

.....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box <input type="checkbox"/>	
The priority of the following earlier application(s) is hereby claimed:			
Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) GB	12.05.94 (12 May 1994)	9409496.8	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / _____

Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office): Date (day/month/year): Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request : 3 sheets
2. description : 11 sheets
3. claims : 3 sheets
4. abstract : 1 sheets
5. drawings : 6 sheets

Total : 24 sheets

This international application is accompanied by the item(s) marked below:

1. <input type="checkbox"/> separate signed power of attorney	5. <input checked="" type="checkbox"/> fee calculation sheet
2. <input type="checkbox"/> copy of general power of attorney	6. <input type="checkbox"/> separate indications concerning deposited microorganisms
3. <input type="checkbox"/> statement explaining lack of signature	7. <input type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette)
4. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):	8. <input type="checkbox"/> other (specify): _____

Figure No. 6 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

RAE, Patricia A.
Patent Agent
Sim & McBurney

For receiving Office use only

1. Date of actual receipt of the purported international application:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority ISA /

6. Transmittal of search copy delayed until search fee is paid

2. Drawings:

received:

not received:

For International Bureau use only

Date of receipt of the record copy
by the International Bureau:

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JUL 11 1995

SIM & MCBURNEY
SIM, HUGHES, ASHTON & MCKAY

PCT

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

RAE, Patricia, A.
Sim & McBurney
701 - 330 University Avenue
Toronto, Ontario M5G 1R7
CANADA

Date of mailing: 05 July 1995 (05.07.95)		
Applicant's or agent's file reference: 4767-49/PAR		IMPORTANT NOTIFICATION
International application No.: PCT/CA95/00287	International filing date: 12 May 1995 (12.05.95)	Priority date: 12 May 1994 (12.05.94)
Applicant: LONDON HEALTH ASSOCIATION et al		

The applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to the following application(s):

Priority application No:	Priority date:	Priority country:	Date of receipt of priority document:
9409496.8	12 May 1994 (12.05.94)	GB	04 Jul 1995 (04.07.95)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorised officer: M. Lee Telephone No.: (41-22) 730.91.11
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PCT/CA95/00287

JUN 6 1995

PATENT COOPERATION TREATY**SIM & MCBURNEY
SIM, HUGHES, ASHTON & MCKAY****PCT****NOTIFICATION OF RECEIPT OF
RECORD COPY**

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU**To:**

RAE, Patricia, A.
Sim & McBurney
701 - 330 University Avenue
Toronto, Ontario M5G 1R7
CANADA

Date of mailing (day/month/year) 31 May 1995 (31.05.95)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 4767-49/PAR	International application No. PCT/CA95/00287

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

LONDON HEALTH ASSOCIATION (for all designated States except US)
DUPRE, John (for US)

International filing date : 12 May 1995 (12.05.95)
Priority date(s) claimed : 12 May 1994 (12.05.94)
Date of receipt of the record copy by the International Bureau : 30 May 1995 (30.05.95)

Designated Offices which will be notified of the receipt of the record copy :

AP :KE,MW,SD,SZ,UG
EP :AT,BE,CH,DE,DK,ES,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,ML,MR,NE,SN,TD,TG
National :AM,AT,AU,BB,BG,BR,BY,CA,CH,CN,CZ,DE,DK,EE,ES,FI,GB,GE,HU,IS,JP,KE,KG,KP,
KR,KZ,LK,LR,LT,LU,LV,MD,MG,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,TJ,TM,TT,UA,
UG,US,UZ,VN

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

time limits for entry into the national phase;
 confirmation of precautionary designations;
 requirements regarding priority documents.

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: M. Lee  Telephone No. (41-22) 730.91.11
Facsimile No. (41-22) 740.14.35	

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiry of 19 months from the priority date. A further extension of time or grace period, in some cases upon payment of an additional fee, is available in some designated (or elected) Offices.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

Note that since CH/LI, ES and GR are not bound by PCT Chapter II (which provides for the international preliminary examination procedure), those States cannot be elected in a demand for international preliminary examination. In the case of designations of CH/LI or ES for a national patent, the applicant must thus always enter the national phase before the national Offices of those States before the expiry of 20 months from the priority date. In the case of designations of CH/LI, ES or GR for a European patent, however, the 31-month time limit applies in respect of those designations if at least one other State designated for a European patent is also elected within the 19-month period.

Note also that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents the following is recalled.

Where the priority of an earlier national (i.e., national or regional) application is claimed, the applicant must submit a copy of the said national application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date (Rule 17.1).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such a request must be made before the expiration of the 16-month time limit.

It is recalled that, where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

If the priority document concerned is not submitted to the International Bureau before the expiration of the 16-month time limit, or if the request to the receiving Office to transmit the priority document has not been made (and the corresponding fee, if any, paid) before the expiration of this time limit, any designated State may disregard the priority claim.

PATENT COOPERATION TREATY

RECEIVED

FEB 15 1996

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

SIM & MCBURNEY
SIM, HUGHES, ASHTON & MCK

To:

RAE, Patricia A.
Sim & McBurney
330 University Avenue
Suite 701
Toronto, Ontario M5G 1R7
CANADA

WRITTEN OPINION

(PCT Rule 66)

		Date of mailing (day/month/year)	12. Feb. 1996
Applicant's or agent's file reference 4767-49/PAR		REPLY DUE	within 3 months/ days from the above date of mailing
International application No. PCT/CA 95/ 00287	International filing date (day/month/year) 12/05/1995	Priority date (day/month/year) 12/05/1994	
International Patent Classification (IPC) or both national classification and IPC A61K38/26			
Applicant LONDON HEALTH ASSOCIATION et al.			

1. This written opinion is the first (first, etc.) drawn up by this International Preliminary Examining Authority.
2. This report contains indications and corresponding pages relating to the following items:

I Basis of the opinion
II Priority
III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV Lack of unity of invention
V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI Certain documents cited
VII Certain defects in the international application
VIII Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

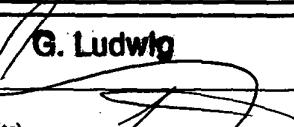
When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 12/09/1996

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Examiner  G. Ludwig
	Formalities officer (incl. extension of time limits) Telephone No. <u>089/1111</u>

WRITTEN OPINION

Intern. application No.

PCT/CA95/00287

I. Basis of the opinion

1. This opinion has been drawn up on the basis of (Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".):

the international application as originally filed.

the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,

the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,

the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,

2. The amendments have resulted in the cancellation of:

the description, pages _____.
 the claims, Nos. _____.
 the drawings, sheets/fig _____.

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

WRITTEN OPINION

Intern. application No.

PCT/CA95/00287

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

the entire international application,

claims Nos. 1-12 _____

because:

the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination (specify):

the description, claims or drawings (indicate particular elements below) or said claims Nos. 1-12 _____ are so unclear that no meaningful opinion could be formed (specify):

1. According to the WHO-classification insulin-dependent diabetes mellitus (IDDM) is called type I diabetes whereas non-insulin requiring diabetes (NIDDM) is called type II diabetes.

Claim 4 relates to type I diabetes whereas claim 1 upon which claim 4 depends refers to insulin-requiring diabetes.

The distinction between type I diabetes and insulin-requiring diabetes in these claims appears to contradict the WHO-definition.

This objection also holds, mutatis mutandis, for claims 10-11.

2. Claim 5 refers to type II diabetes as an insulin-requiring diabetes.

WRITTEN OPINION

Intern. application No.

PCT/CA95/00287

This definition appears to contradict the WHO definitions as indicated above according to which type II diabetes is a non-insulin dependent diabetes.

The corresponding passage of the description related to claim 5 appears to be on page 7, lines 25-27.

3. With respect to the above objections an explanation of the applicant is needed.

the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos. _____.

WRITTEN OPINION

Intern. application No.

PCT/CA95/00287

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Industrial Applicability (IA) Claims _____
 Claims _____

2. CITATIONS AND EXPLANATIONS

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 91/11457

D2: The New England Journal of Medicine 326, 1316-1322 (1992)

D3: The Journal of Clinical Investigation 93, 2263-2266
(1994)

2. Document D1 discloses the use of glucagon-like peptide 1 (7-36 or 7-37) [GLP-1 or GLIP] or amides thereof for the treatment of type II diabetes.

Document D2 discloses that GLIP (amide) may be useful in the treatment of type II diabetes (NIDDM).

It also states that GLIP (amide) infusion decreases the meal-related insulin requirement in type I diabetes (IDDM) patients. However, the treatment of type I diabe-

tes by GLIP does not appear to be suggested by D2.

Document D3 discloses that GLIP (amide) increases glucose effectiveness (relevant for type II diabetes) and that it also increases insulin secretion (relevant for type I diabetes). However, the cautious conclusions of the authors of the end of this basic biochemical/pharmacological study do not appear to suggest the use of GLIP for the treatment of diabetes type I or type II.

3. In view of the above it appears that the state of the art does not suggest a treatment of type I diabetes (IDDM) by GLIP.

Claims 13-14 are therefore considered as novel and inventive.

4. For the assessment of the presently worded claims 1-5 and 13 on the question whether it is industrially applicable, no unified criteria exist in the PCT. In the Contracting States of the PCT the patentability of such a claim can also depend on its formulation. Accordingly, the applicant is informed that under the EPC these claims would not be allowable (Art. 52(4) & 52(1) EPC).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. There appears to be no essential technical difference between claim 7 and claim 6. The former claim should therefore be deleted for the sake of conciseness.

This objection also holds, *mutatis mutandis*, for claims 8-9.

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 4767-49/PAR:ba
International application No. PCT/CA95/00287	International filing date (day/month/year) 12 May 1995 (12.05.95)	(Earliest) Priority date (day/month/year) 12 May 1994 (12.05.94)
Title of invention TREATMENT OF DIABETES		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LONDON HEALTH ASSOCIATION P.O. Box 5339 London, Ontario N6A 5A5 Canada		Telephone No.: (519) 663-3300
		Facsimile No.: (519) 663-3232
		Teleprinter No.:
State (i.e. country) of nationality: CA	State (i.e. country) of residence: CA	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) DUPRE, John 72 Sherwood Avenue London, Ontario N6A 2E2 Canada		
State (i.e. country) of nationality: CA	State (i.e. country) of residence: CA	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) 		
State (i.e. country) of nationality: 	State (i.e. country) of residence: 	
<input type="checkbox"/> Further applicants are indicated on a continuation sheet.		

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is agent common representative
 and has been appointed earlier and represents the applicant(s) also for international preliminary examination.
 is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
 is hereby appointed, specifically to: the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>	Telephone No.:
Rae, Patricia A. SIM & McBUPNEY 701 - 330 University Avenue Toronto, Ontario M5G 1R7 Canada	(416) 595-1155
	Facsimile No.:
	(416) 595-1163
	Telex/Teletype No.:

Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

- (i) to start the international preliminary examination on the basis of the international application as originally filed.
- (ii) to take into account the amendments under Article 34 of
 - the description (amendments attached).
 - the claims (amendments attached).
 - the drawings (amendments attached).
- (iii) to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).
- (iv) to disregard any amendments of the claims made under Article 19 and to consider them as reversed.
- (v) to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

- * Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT) except*

.....
.....
.....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

1. amendments under Article 34

description : sheets
claims : sheets
drawings : sheets

2. letter accompanying amendments under Article 34 : sheets

3. copy of amendments under Article 19 : sheets

4. copy of statement under Article 19 : sheets

5. other (specify): : sheets

For International Preliminary Examining Authority use only

received not received

<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

1. separate signed power of attorney
2. copy of general power of attorney
3. statement explaining lack of signature

4. fee calculation sheet
5. other (specify):

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Rae, Patricia A.
SIM & McBURNEY

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. The applicant has been informed accordingly.

4. The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/CA95/00287	For International Preliminary Examining Authority use only									
Applicant's or agent's file reference 4767-49/PAR:ba	Date stamp of the IPEA									
<p>Applicant London Health Association</p> <p>Calculation of prescribed fees</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;">Preliminary examination fee</td> <td style="width: 10%; text-align: center;">DM 3,000</td> <td style="width: 20%; text-align: right;">P</td> </tr> <tr> <td>2. Handling fee</td> <td style="text-align: center;">DM 270</td> <td style="text-align: right;">H</td> </tr> <tr> <td>3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box</td> <td style="text-align: center;">DM 3,270</td> <td style="text-align: center;">TOTAL</td> </tr> </table>		Preliminary examination fee	DM 3,000	P	2. Handling fee	DM 270	H	3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	DM 3,270	TOTAL
Preliminary examination fee	DM 3,000	P								
2. Handling fee	DM 270	H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	DM 3,270	TOTAL								
<p>Mode of Payment</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> authorization to charge deposit account with the IPEA (see below) <input type="checkbox"/> cheque <input type="checkbox"/> postal money order <input checked="" type="checkbox"/> bank draft </td> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> cash <input type="checkbox"/> revenue stamps <input type="checkbox"/> coupons <input type="checkbox"/> other (specify): _____ </td> </tr> </table>		<input type="checkbox"/> authorization to charge deposit account with the IPEA (see below) <input type="checkbox"/> cheque <input type="checkbox"/> postal money order <input checked="" type="checkbox"/> bank draft	<input type="checkbox"/> cash <input type="checkbox"/> revenue stamps <input type="checkbox"/> coupons <input type="checkbox"/> other (specify): _____							
<input type="checkbox"/> authorization to charge deposit account with the IPEA (see below) <input type="checkbox"/> cheque <input type="checkbox"/> postal money order <input checked="" type="checkbox"/> bank draft	<input type="checkbox"/> cash <input type="checkbox"/> revenue stamps <input type="checkbox"/> coupons <input type="checkbox"/> other (specify): _____									
<p>Deposit Account Authorization (this mode of payment may not be available at all IPEAs)</p> <p>The IPEA _____ <input type="checkbox"/> is hereby authorized to charge the total fees indicated above to my deposit account.</p> <p><input type="checkbox"/> (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.</p>										
Deposit Account Number	Date (day/month/year)	Signature								

PATENT COOPERATION TRAJECTORY

RECEIVED

AUG 11 1995

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

SIM & McBURNEY
SIM, HUGHES, ASHTON & MCKAY

To:
 Sim & McBurney
 Attn. RAE, Patricia A.
 330 University Avenue
 Suite 701
 Toronto, Ontario M5G 1R7
 CANADA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

		Date of mailing (day/month/year) 07/08/95
Applicant's or agent's file reference 4767-49/PAR	FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/CA95/00287	International filing date (day/month/year) 12/05/95	
Applicant LONDON HEALTH ASSOCIATION et al.		

1. The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? To the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2; the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Zorka Bota
---	--------------------------------------

NOTES TO FORM PCT/ISA/220

These notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers;
Claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 TO 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings which cannot be amended under Article 19(1).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4767-49/PAR	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/CA95/00287	International filing date (day/month/year) 12/05/95	(Earliest) Priority Date (day/month/year) 12/05/94
Applicant LONDON HEALTH ASSOCIATION et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title, the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:

Figure No. _____

 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA95/00287

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-5, 13 because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-5, 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 95/00287

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K38/26 // (A61K38/26, 38:28)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-91 11457 (BUCKLEY D. ET AL.) 8 August 1991 see the whole document ---	1,5,6
X	THE JOURNAL OF CLINICAL INVESTIGATION, vol. 93, no. 5, May 1994 pages 2263-2266, D'ALESIO D.A. ET AL. 'Glucagon-like Peptide 1 Enhances Glucose Tolerance Both by Stimulation of Insulin Release and by Increasing Insulin-independent Glucose Disposal' see the whole document ---	1-14 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'B' earlier document but published on or after the international filing date
- *'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *'O' document referring to an oral disclosure, use, exhibition or other means
- *'P' document published prior to the international filing date but later than the priority date claimed

- *'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- *'&' document member of the same patent family

1

Date of the actual completion of the international search

Date of mailing of the international search report

24 July 1995

07.08.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Moreau, J

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE NEW ENGLAND JOURNAL OF MEDICINE , vol. 326, no. 20, 14 May 1992 BOSTON (US), pages 1316-1322, GUTNIAK M. ET AL. 'Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus' cited in the application see the whole document ----	1-14
A	WO-A-93 25579 (PFIZER INC.) 23 December 1993 see the whole document -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/CA 95/00287

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9111457	08-08-91	EP-A-	0512042	11-11-92
WO-A-9325579	23-12-93	AU-B-	4027593	04-01-94
		CA-A-	2138161	23-12-93
		CN-A-	1085913	27-04-94
		EP-A-	0646128	05-04-95
		HU-A-	64367	28-12-93
		JP-T-	7504679	25-05-95
		NO-A-	944853	14-12-94

INTERNATIONAL COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4767-49/PAR	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/CA95/00287	International filing date (<i>day/month/year</i>) 12/05/95	(Earliest) Priority Date (<i>day/month/year</i>) 12/05/94
Applicant LONDON HEALTH ASSOCIATION et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.
 It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title, the text is approved as submitted by the applicant.
 the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 Figure No. _____
 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA95/00287

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-5, 13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-5, 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
/CA 95/00287A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/26 // (A61K38/26, 38:28)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-91 11457 (BUCKLEY D. ET AL.) 8 August 1991 see the whole document ---	1,5,6
X	THE JOURNAL OF CLINICAL INVESTIGATION, vol. 93, no. 5, May 1994 pages 2263-2266, D'ALESIO D.A. ET AL. 'Glucagon-like Peptide 1 Enhances Glucose Tolerance Both by Stimulation of Insulin Release and by Increasing Insulin-independent Glucose Disposal' see the whole document ---	1-14

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

1

Date of the actual completion of the international search 24 July 1995	Date of mailing of the international search report 07.08.95
---	--

Name and mailing address of the ISA
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Fax (+31-70) 340-3016

Authorized officer

Moreau, J

INTERNATIONAL SEARCH REPORT

International Application No
CA 95/00287

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE NEW ENGLAND JOURNAL OF MEDICINE , vol. 326, no. 20, 14 May 1992 BOSTON (US), pages 1316-1322, GUTNIAK M. ET AL. 'Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus' cited in the application see the whole document ----	1-14
A	WO-A-93 25579 (PFIZER INC.) 23 December 1993 see the whole document -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 95/00287

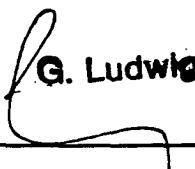
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9111457	08-08-91	EP-A-	0512042	11-11-92
WO-A-9325579	23-12-93	AU-B-	4027593	04-01-94
		CA-A-	2138161	23-12-93
		CN-A-	1085913	27-04-94
		EP-A-	0646128	05-04-95
		HU-A-	64367	28-12-93
		JP-T-	7504679	25-05-95
		NO-A-	944853	14-12-94

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4767-49/PAR	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA 95/00287	International filing date (day/month/year) 12/05/1995	Priority date (day/month/year) 12/05/1994	
International Patent Classification (IPC) or national classification and IPC A61K38/26			
Applicant VICTORIA/UNIVERSITY HOSPITAL CORP. et al.			

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consists of a total of 1 sheets.</p> <p>3. This report contains indications and corresponding pages relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 04/12/1995	Date of completion of this report 25. Juni 1996
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  G. Ludwig Telephone No. 089/1996

INTERNATIONAL PRELIMINARY EXAMINATI

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/CA95/00287

V. Reasoned statement under Article 35(2) with regard to citations and explanations supporting such statement

1. STATEMENT

Novelty (N) Claims 1-9,
Claims 10__

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

[] the international application as originally filed.

Inventive Step (IS) Claims 4, 8
Claims 1-3,

[x] the description, pages 1-11_____, as originally filed,
pages_____, filed with the demand,
pages_____, filed with the letter of_____,
pages_____, filed with the letter of_____

Industrial Applicability (IA) Claims 1-14
Claims ____

[x] the claims, Nos. 1-5, 6(part), 13(part)-14_____, as originally filed,
Nos._____, as amended under Article 19,
Nos._____, filed with the demand,
Nos. 6(part), 7-12, 13(part)_____, filed with the letter of 10.5.96_____,
Nos._____, filed with the letter of_____

2. CITATIONS AND EXPLANATIONS

1. The following documents (port:

D1: WO 91/11457

D2: The New England Journ
(1992)D3: The Journal of Clinic
(1994)

[] the drawings, sheets/fig_____, as originally filed,
sheets/fig_____, filed with the demand,
sheets/fig_____, filed with the letter of_____,
sheets/fig_____, filed with the letter of_____

2. The amendments have resulted in the cancellation of:

[] the description, pages_____.

[] the claims, Nos._____.

[] the drawings, sheets/fig_____.

3. [] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

This is normally not the non-insulin requiring dia type II diabetes.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Of diagnosed diabetes about 55% appears to be NIDDM not treated with insulin and about 30% is NIDDM treated with insulin.

2.1 "Insulin-requiring diabetes" as used in the claims of the specification can be understood to refer to all diabetics which are unable to avoid hyperglycemia without the use of insulin.

This term therefore encompasses both type I (IDDM) and type II (NIDDM) diabetes.

3. Document D1 discloses the use of glucagon-like peptide 1 (7-36 or 7-37) [GLP-1 or GLIP] or amides thereof for the treatment of type II diabetes.

Document D2 discloses that GLIP (amide) may be useful in the treatment of type II diabetes (NIDDM).

Document D2 states that a better treatment for patients with NIDDM who do not respond to sulfonylurea therapy would be one that decreased their requirement for insulin and therefore decreased the occurrence of hyperinsulinemia. The study of D2 demonstrates that at least in the short term, the administration of GLIP decreases postpranial insulin requirements and plasma insulin concentrations in patients with NIDDM. Therefore this peptide may have a role in the treatment of some patients with diabetes.

Although document D2 shows, inter alia, that in patients with IDDM infusion of GLIP decreased the calculated isoglycemic meal-related insulin requirement a potential use of GLIP for the treatment of IDDM (type I diabetes) patients is not indicated in this study.

Document D3 discloses that GLIP (amide) increases glucose effectiveness (relevant for type II diabetes) and that it also increases insulin secretion (relevant for type I diabetes). However, the cautious conclusions of the authors of the end of this basic biochemical/pharmacological study do not appear to suggest the use of GLIP for the treatment of diabetes type I or type II.

4. In view of the above it appears that the state of the art does not suggest a treatment of type I diabetes (IDDM) by GLIP.

Claims 4, 8, 11 and 13-14 are therefore considered as novel and inventive.

5. It appears that the skilled man, starting from document D1 and having regard to documents D2-D3, wanting to provide a further (improved) treatment of NIDDM (type II diabetes) would want to use GLIP, alone or in combination with insulin for the treatment of this disease.

Claims 1, 5-6 and 9-10 are therefore not inventive. Accordingly, this also holds for the dependent claims 2-3, 7 and 12.

6. For the assessment of the presently worded claims 1-5 and 13 on the question whether it is industrially applicable, no unified criteria exist in the PCT. In the Contracting States of the PCT the patentability of such a claim can also depend on its formulation. Accordingly, the applicant is informed that under the EPC these claims would not be allowable (Art. 52(4) & 52(1) EPC).

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 38/26 // (A61K 38/26, 38:28)		A1	(11) International Publication Number: WO 95/31214 (43) International Publication Date: 23 November 1995 (23.11.95)
(21) International Application Number: PCT/CA95/00287 (22) International Filing Date: 12 May 1995 (12.05.95) (30) Priority Data: 9409496.8 12 May 1994 (12.05.94) GB		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(71) Applicant (for all designated States except US): LONDON HEALTH ASSOCIATION [CA/CA]; P.O. Box 5339, London, Ontario N6A 5A5 (CA). (72) Inventor; and (75) Inventor/Applicant (for US only): DUPRE, John [CA/CA]; 72 Sherwood Avenue, London, Ontario N6A 2E2 (CA). (74) Agent: RAE, Patricia, A.; Sim & McBurney, 701-330 University Avenue, Toronto, Ontario M5G 1R7 (CA).		Published With international search report.	
(54) Title: TREATMENT OF DIABETES			
(57) Abstract <p>A method is provided for treating insulin-requiring diabetes by a regimen including administration of insulin and glucagon-like insulinotropic peptide or a related peptide.</p>			

TREATMENT OF DIABETESField of the Invention

The present invention relates to methods and
5 compositions for treatment of diabetes.

Background of the Invention

The recent findings of the Diabetes Control and Complications Trial (DCCT) carried out by the U.S. 10 National Institute of Health have emphasised the importance of doing everything possible to normalise blood glucose levels in diabetics to avoid or delay micro-vascular damage. Intensified insulin therapy has been shown by the trial to improve glycaemic control but 15 is accompanied by the risk of hypoglycaemia. This limits the degree of glycaemic control which can be safely attempted, so that true normalisation of blood glucose levels cannot be achieved with insulin therapy alone.

Glucagon-like peptide 1(7-36)amide or glucagon-like 20 insulinotropic peptide (GLIP) is a gastrointestinal peptide which potentiates insulin release in response to glycaemia in normal humans.

Glucagon-like insulinotropic peptide has been suggested for use either alone or in conjunction with 25 oral hypoglycaemic agents in Type II or non-insulin dependent diabetes (Gutniak et al., (1992), N.E.J.M. vol. 326, p. 1316; International Patent Application No. WO93/18786). These authors have noted a synergistic effect between the peptide and oral hypoglycaemic agents 30 in Type II diabetics.

The present inventor has found, unexpectedly, that administration of glucagon-like insulinotropic peptide permits improved glycaemic control in subjects with insulin-requiring diabetes.

Summary of Invention

In accordance with one embodiment of the present invention, a method is provided for treating insulin-requiring diabetes in a mammal comprising 5 administering to the mammal in a suitable regimen an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);
- 10 (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b).

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from 15 the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b)

is used for the preparation of a medicament for use in 20 the treatment of insulin-requiring diabetes in a suitable regimen which additionally comprises treatment with insulin.

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from 25 the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b)

is used for the preparation of a medicament which also 30 includes insulin for treatment of insulin-requiring diabetes.

In accordance with a further embodiment of the invention, a pharmaceutical composition is provided for the treatment of insulin-requiring diabetes comprising 35 an effective amount of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);

- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b) and a pharmaceutically acceptable carrier.

In accordance with a further embodiment of the
5 invention, a method is provided for treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);
- 10 (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b).

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from
15 the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b)

is used for the preparation of a medicament for use in
20 the treatment of Type I diabetes.

Summary of Drawings

Figure 1A shows blood levels of glucose, Figure 1B shows C-peptide, Figure 1C shows human pancreatic
25 polypeptide (HPP), Figure 1D shows glucagon and Figure 1E shows gastrin in Type I diabetic subjects after Sustacal meal alone (○) or Sustacal meal with GLIP infusion (●).

Figure 2A shows blood levels of glucose and Figure 2B C-peptide in Type I diabetic subjects during glucose
30 infusion alone (○) or along with IV GLIP(●).

Figure 3A shows blood levels of glucose (expressed as the change (Δ) from baseline values at time zero) and Figure 3B shows C-peptide (expressed as the change (Δ) from baseline values at time zero) in Type I diabetic subjects after Sustacal meal and saline infusion (○) or Sustacal meal with infusion of 0.75 pm GLIP/kg/min (▲).

Figure 4A shows blood levels of glucose, Figure 4B shows C-peptide, Figure 4C shows insulin and Figure 4D shows human pancreatic polypeptide (HPP) in normal subjects after Sustacal meal alone (O) or Sustacal meal 5 immediately preceded by a subcutaneous injection of 100 µg GLIP (●).

Figure 5A shows blood levels of glucose, Figure 5B shows C-peptide, Figure 5C shows insulin and Figure 5D shows human pancreatic polypeptide (HPP) in Type I 10 diabetic subjects after Sustacal meal alone (O) or Sustacal meal immediately preceded by a subcutaneous injection of 100 µg GLIP (●).

Figure 6A shows blood levels of glucose, Figure 6B shows C-peptide, Figure 6C shows insulin, Figure 6D shows 15 human pancreatic polypeptide (HPP), Figure 6E shows GLIP (GLIP-1) and Figure 6F gastrin in a Type I diabetic subject who received 5 Units regular human insulin and 50 µg GLIP subcutaneously prior to a Sustacal meal.

Detailed Description of the Invention

20 The glucagon-like peptide 1 fragments, glucagon-like peptide 1(7-36)amide and glucagon-like peptide 1(7-37), show essentially similar insulinotropic and other biochemical effects in humans and other mammals.

25 Glucagon-like peptide 1(7-36)amide is referred to herein as GLIP.

The present invention provides a method of treating Type I diabetes by administration of an effective amount of GLIP, or other glucagon-like peptide 1-related peptide, either alone or in conjunction with a regimen of 30 insulin administration.

35 Although the discussion herein refers to use of "GLIP", it will be understood by those skilled in the art that the therapeutic methods of the invention may be practised by employing GLIP, glucagon-like peptide 1(7-37), an effective peptide including GLIP or glucagon-like peptide 1(7-37), or an effective fragment or analogue of GLIP or glucagon-like peptide 1(7-37).

As is seen in Figure 2, IV administration of GLIP along with intravenous glucose stimulated secretion of endogenous insulin in the subjects studied and gave improved control of blood glucose level. These subjects 5 were in the remission phase, or so-called "honeymoon phase", of IDDM characterised by substantial remaining endogenous insulin secretion.

The same dose of GLIP (1.2 pm/kg/min) gave excellent control of blood glucose level in these subjects after a 10 meal, as seen in Figure 1, Panel A. Under these conditions, GLIP infusion also prevented a significant increase in blood levels of C-peptide.

After the Sustacal meal, the test subjects showed normal secretion of pancreatic polypeptide (PP) but this 15 response was absent during GLIP infusion (Figure 1, Panel C). It is believed that this abrogation of PP response was due to the delayed passage of the meal from the stomach to the small intestine as a result of GLIP administration. That it was not due to a general 20 suppression of gastrointestinal peptide secretion is indicated by the normal gastrin response to the presence of food in the stomach in these subjects (Figure 1, Panel E).

Administration of GLIP prevented the mean rise in 25 plasma glucagon levels stimulated by the meal in the absence of GLIP. Gastrin levels were not significantly affected.

Administration of a lower dose of GLIP (0.75 pmol/kg/min) along with a meal resulted in some increase 30 in blood glucose and C-peptide, as seen in Figure 3. Although the increase in glucose was less than in the control experiment, the rise in C-peptide was similar to the control experiment.

GLIP is known to cause delay of gastric emptying in 35 humans and other mammals (Wettergren et al., (1993), Digestive Diseases and Sciences, v. 38, p. 665). As seen in Figure 4, when GLIP is given subcutaneously to normal

subjects prior to ingestion of a meal, there is a delay of 30 to 60 minutes in the rise in blood glucose level. This delay is likely due to inhibition of gastric emptying.

5 When Type I diabetics were given GLIP subcutaneously prior to ingestion of a test meal, a lowering of blood glucose levels was seen compared to the control figures when no GLIP was administered (Figure 5, Panel A). The delayed rise in pancreatic polypeptide (HPP) levels 10 (Panel D) indicate delayed gastric emptying. As seen from Panels B and C, there was no enhancement of insulin secretion over control levels to account for the lower glucose levels.

15 It may be that the improved glycaemic control seen with GLIP administration in Type I diabetics is due to delay of the post-meal rise in blood glucose through the interval required for the establishment of the effect of insulin.

20 The efficacy of GLIP administration along with insulin in restraining the expected rise in blood glucose after a standard meal in Type I diabetes is seen in Example 6 and Figure 6. 50 µg GLIP was administered along with half the insulin dose that would usually be required to deal with the test meal. As seen in Figure 25 6, Panel A, blood glucose did not rise above 8 mM. With this size of meal and half the usual insulin dose, considerably higher blood glucose levels would have been expected, in the absence of the effect of GLIP. For example, with this meal and no insulin, blood glucose 30 levels reached 15 mM, as seen in Figure 5, Panel A.

As seen from Figure 6, Panel E, GLIP was cleared from the blood in about two hours so that pre-meal GLIP administration would not be expected to interfere with management of subsequent meals.

35 When GLIP is used to improve glycaemic control in Type I diabetics having residual endogenous insulin secretion capacity, both the insulinotropic effect of the

hormone and its effect to delay gastric emptying will contribute to its effect. Some remission phase Type I subjects may be sufficiently controlled by administration of GLIP alone, without exogenous insulin.

5 In the majority of patients with Type I diabetes, however, treatment with a regimen including both GLIP and insulin is likely to be required. These studies indicate that the observed effects of GLIP on glycaemia are not dependent on stimulation of insulin release and are
10 therefore not limited to diabetics retaining residual insulin secreting capacity.

15 The use of GLIP in treating Type I diabetes, in accordance with the present invention, provides improved glycaemic control and reduces post-prandial excursions of blood glucose. This accords with the current emphasis on normalising blood glucose levels as much as possible, to reduce diabetic complications.

20 Furthermore, a regimen combining administration of insulin and administration of GLIP, in accordance with the present invention, is applicable to patients with insulin requiring diabetes which would not strictly be classified as Type I.

25 An insulin-requiring diabetic is a diabetic who is unable to avoid hyperglycaemia without the use of insulin. The invention further provides a method for treating patients with diabetes which is etiologically Type II but requires insulin treatment.

30 Diabetics frequently find the requirements for food intake and insulin administration at midday particularly irksome and an interference with work and other activities. By administering GLIP to diabetic subjects at breakfast time, along with administration of longer acting insulin if necessary, diabetics may be able to omit lunch or greatly reduce the size of that meal, and
35 thereby avoid the need for midday insulin.

The delayed adsorption of nutrients when both GLIP and insulin are administered before breakfast will also reduce the risk of hypoglycaemia if lunch is delayed.

The studies described herein also indicate that a 5 therapeutic regimen including both GLIP and insulin will in many cases permit the use of reduced doses of insulin. This is also beneficial in the avoidance of hypo-glycaemia.

GLIP or its related peptides which may be employed 10 in the treatment methods described herein may be administered orally, nasally or parenterally. Parenteral administration may be by a variety of routes including subcutaneous or intravenous infusion, and subcutaneous or intravenous injection.

15 The regimen of GLIP or GLIP and insulin administration required to give the desired glycaemic control in a diabetic patient can be readily determined by those skilled in the management of diabetic patients.

As will be understood by those skilled in the art, 20 any suitable insulin preparation may be used in conjunction with GLIP administration in the combined regimen described herein.

Suitable insulins include regular or fast-acting 25 insulin to maintain blood glucose control through the post-prandial interval, with or without addition of longer-acting insulin to maintain blood glucose control through the post-absorptive interval.

The dosages of GLIP required may be optimised for 30 each subject by evaluation of the degree of glycaemic control achieved by trial doses.

Another convenient method of monitoring the level of effect of GLIP on a subject is to monitor the blood level of pancreatic polypeptide in response to trial doses of GLIP.

35 Such dosage and regimen adjustments are now commonplace, for example for diabetics treated with mixtures of fast and slow acting insulins. These mixed

preparations are available in various ratios of fast to slow and an appropriate ratio must be selected for a particular patient by trial doses. One patient may even employ insulin preparations of different ratios to handle 5 varying sizes of meals. By similar testing, a suitable GLIP and insulin regimen may be selected.

GLIP and insulin may be administered separately or may be prepared and administered as a single formulation.

10

EXAMPLES

Example 1

7 subjects with remission phase Type I diabetes were studied after ingestion of a standardised meal of Sustacal (Upjohn) (delivering 30 kg/kg). Subjects 15 continued their normal insulin treatment programme on the day prior to the test and, on the day of the test, omitted their morning insulin injection and arrived fasting at 8:00 am. On one test day they were given the Sustacal meal, followed immediately by initiation of 20 intravenous infusion of GLIP (synthetic human GLIP-(7-36)amide from Peninsula, U.K.) at an infusion rate of 1.2 pm/kg/min. Infusion was continued for 120 minutes. Blood levels of glucose, C-peptide, gastrin, glucagon and HPP were monitored by standard radioimmunoassay methods 25 in samples taken before and at intervals during the study, up to 180 minutes. On another test day, subjects were given the Sustacal meal alone and the same analytes were similarly monitored.

Results are shown in Figure 1.

30

Example 2

Four subjects with remission phase Type I diabetes were studied during intravenous glucose infusion. Subjects prepared for the tests as described in Example 35 1, but received an intravenous infusion of glucose (20 g

over 60 min. constant rate) instead of the Sustacal meal. On one test day, they also received intravenous GLIP for 60 minutes (1.2 pm/kg/min for 60 min.) and on another test day, they received IV glucose alone. Blood levels 5 of glucose and C-peptide were monitored as in Example 1.

The results are shown in Figure 2.

Example 3

10 Four subjects with remission phase Type I diabetes were studied during infusion with 0.75 pm/kg/min GLIP for 120 minutes after a Sustacal meal.

15 The test was conducted as described in Example 1 and blood glucose and C-peptide levels were measured. On a further test day, the subjects were studied during saline infusion after a similar Sustacal meal.

Results are shown in Figure 3.

Example 4

20 7 normal volunteers were studied after ingestion of a Sustacal meal either alone or immediately preceded by a subcutaneous injection of 100 µg GLIP.

25 Results are shown in Figure 4. *indicates statistically significant differences between treatments (p<0.05).

A delay in increase in blood levels of glucose, HPP, C-peptide and insulin was seen. When the experiment was repeated with 50 µg or 200 µg dose of GLIP, proportionally shorter and longer delays, respectively, were seen.

30

Example 5

35 7 Type I diabetic subjects were studied. Subjects omitted their morning insulin injection on the days of the tests and were given a Sustacal meal alone one day and, on another day, a Sustacal meal immediately preceded by a subcutaneous injection of 100 µg GLIP.

The results are shown in Figure 5. *indicates statistically significant differences between treatments ($p<0.05$).

5 Example 6

One Type 1 diabetic subject was given GLIP along with insulin and the effects on post-prandial glycaemia observed. The subject received 5 units of insulin and 50 μ g GLIP as subcutaneous injections immediately prior to 10 ingestion of a Sustacal meal as described in Example 1. The results are shown in Figure 6. Blood levels of GLIP were monitored by a standard radioimmunoassay method.

15 Although only preferred embodiments of the present invention have been described, the present invention is not limited to the features of these embodiments, but includes all variations and modifications within the scope of the claims.

I CLAIM:

1. A method of treating insulin-requiring diabetes in a mammal comprising administering to the mammal in a suitable regimen an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of
 - (a) glucagon-like peptide 1(7-37);
 - (b) glucagon-like peptide 1(7-36)amide; and
 - (c) an effective fragment or analogue of (a) or (b).
2. The method of claim 1 wherein the mammal is a human.
3. The method of claim 2 wherein an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of
 - (a) glucagon-like peptide 1(7-37);
 - (b) glucagon-like peptide 1(7-36)amide; and
 - (c) an effective fragment or analogue of (a) or (b)are administered to the human at a selected time prior to ingestion of a meal.
4. The method of any of claims 1 to 3 wherein the insulin-requiring diabetes is Type I diabetes.
5. The method of any of claims 1 to 3 wherein the insulin-requiring diabetes is Type II diabetes.
6. Use of a peptide comprising a peptide selected from the group consisting of
 - (a) glucagon-like peptide 1(7-37);
 - (b) glucagon-like peptide 1(7-36)amide; and
 - (c) an effective fragment or analogue of (a) or (b)for the preparation of a medicament for use in the treatment of insulin-requiring diabetes in a suitable

regimen which additionally comprises treatment with insulin.

7. Use of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b) for the preparation of a medicament which also includes insulin for treatment of insulin-requiring diabetes.

8. Use of a peptide in accordance with claim 6 wherein the insulin-requiring diabetes is Type I diabetes.

9. Use of a peptide in accordance with claim 7 wherein the insulin-requiring diabetes is Type I diabetes.

10. A pharmaceutical composition for the treatment of insulin-requiring diabetes comprising an effective amount of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b) and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition in accordance with claim 10 for the treatment of Type I diabetes.

12. The pharmaceutical composition of claim 10 or 11 further comprising an effective amount of insulin.

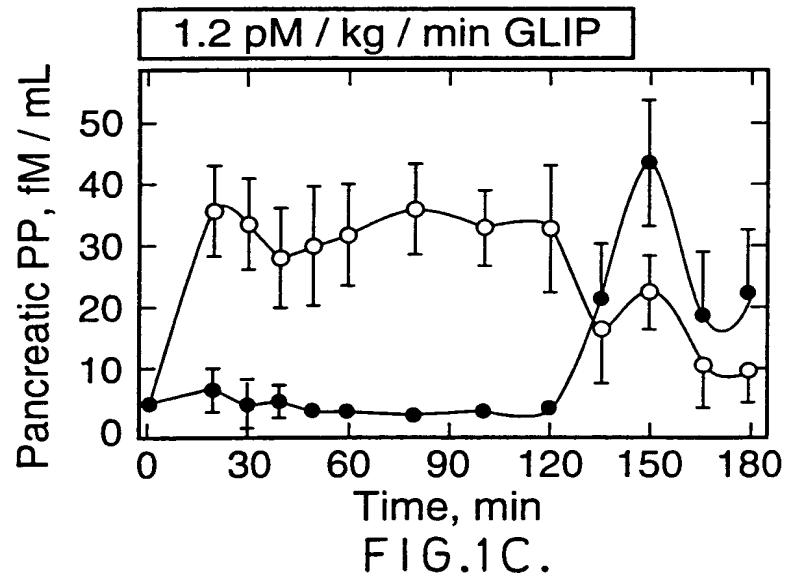
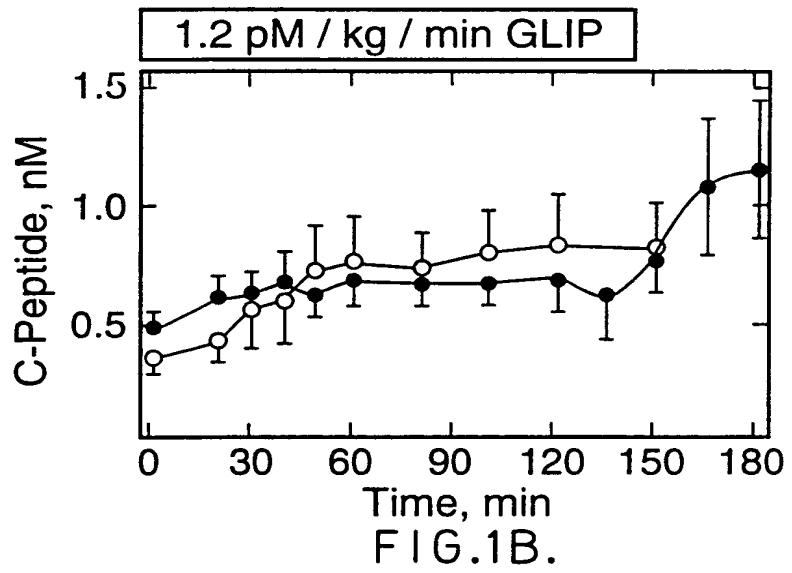
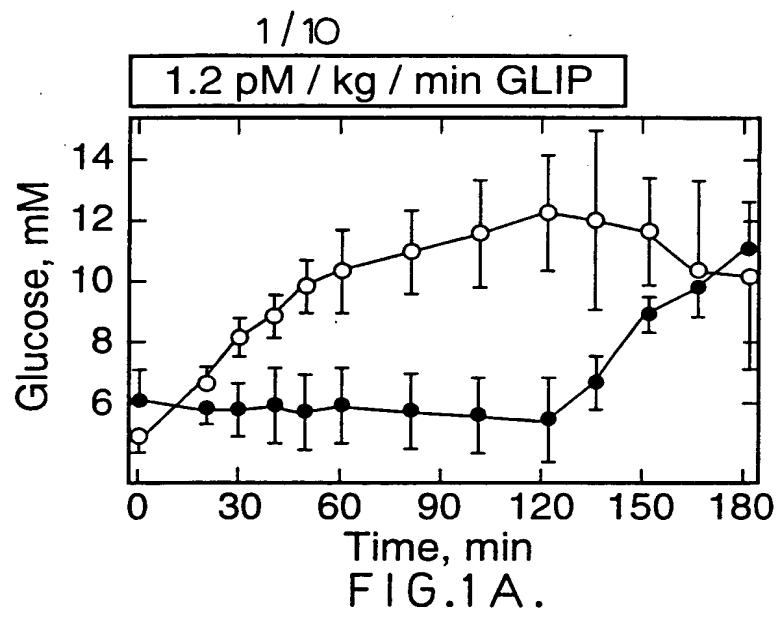
13. A method of treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);

- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b).

14. Use of a peptide comprising a peptide selected from the group consisting of

- (a) glucagon-like peptide 1(7-37);
- (b) glucagon-like peptide 1(7-36)amide; and
- (c) an effective fragment or analogue of (a) or (b) for the preparation of a medicament for use in the treatment of Type I diabetes.



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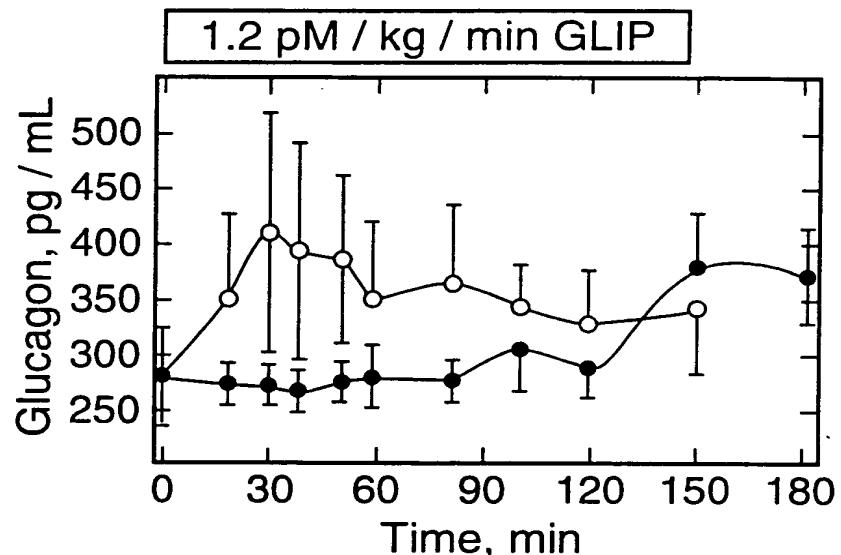


FIG.1D.

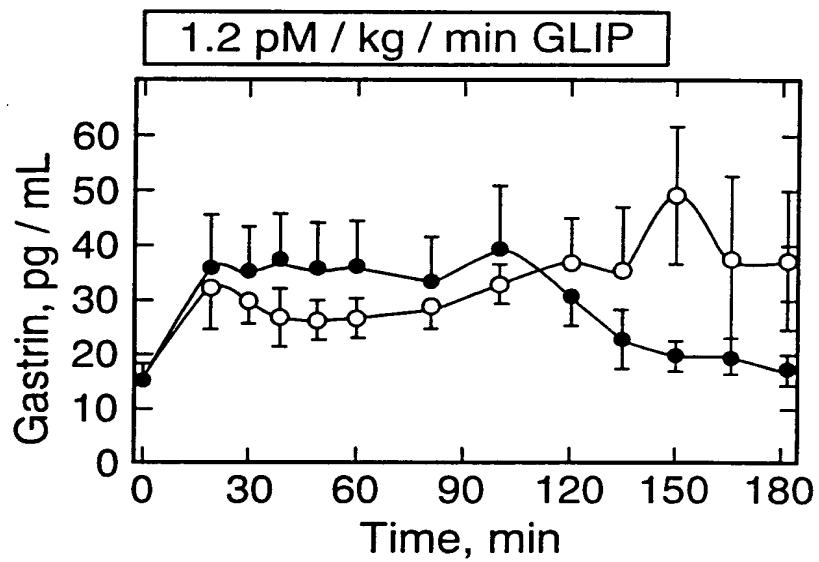


FIG.1E.

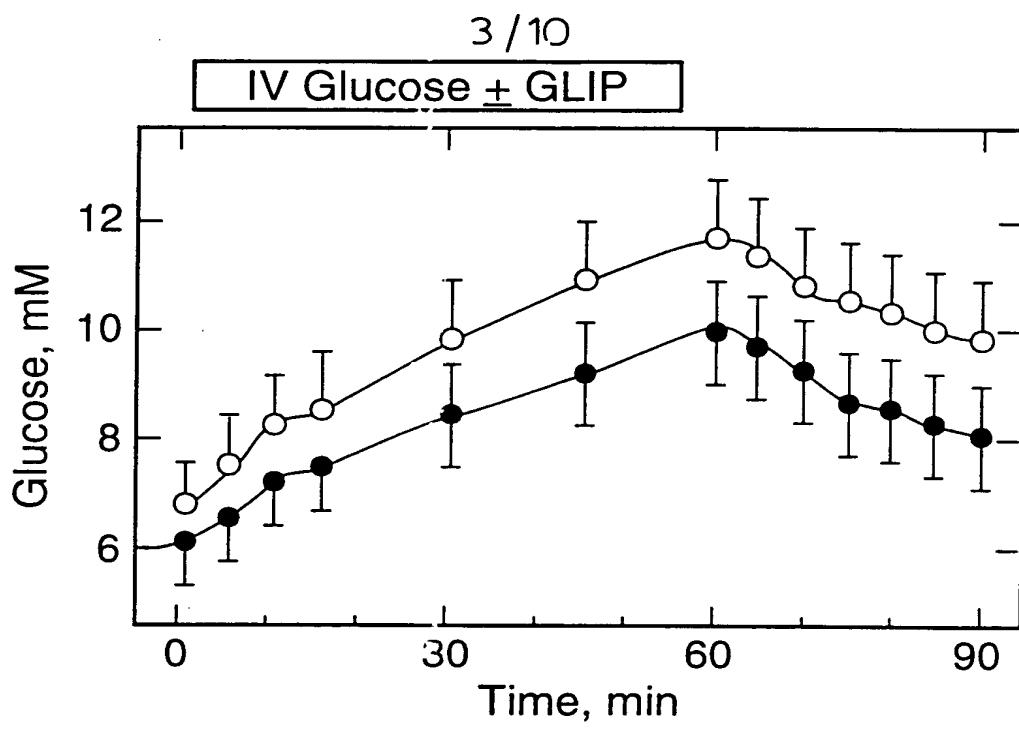


FIG. 2 A.

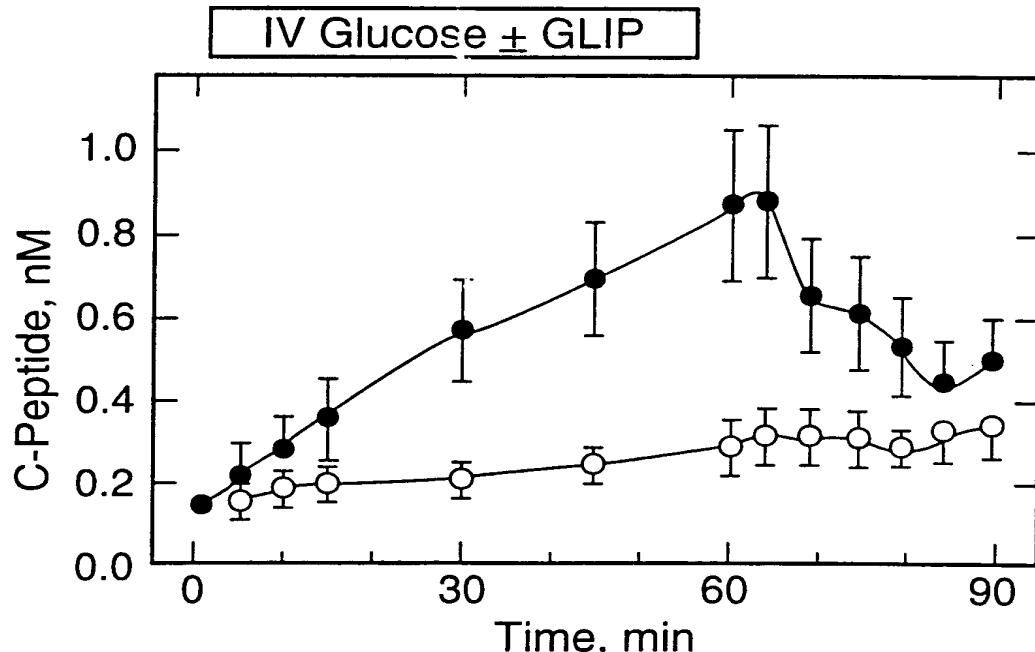


FIG. 2 B.

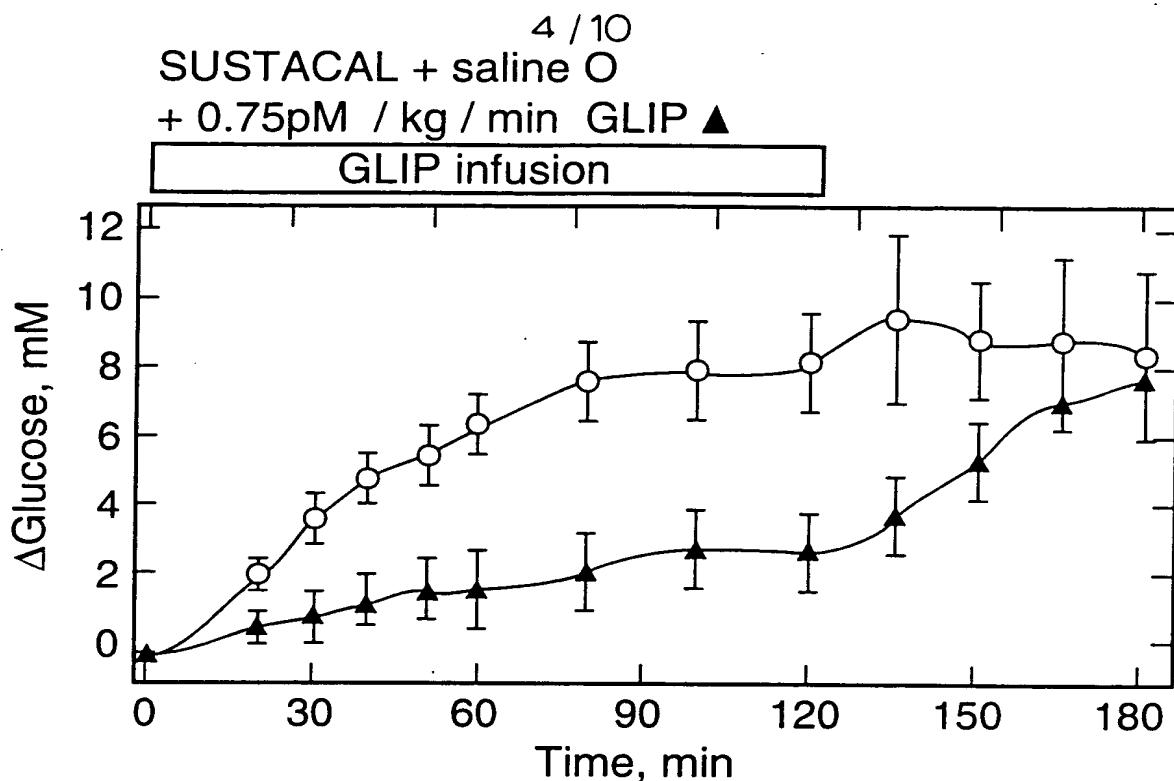


FIG. 3 A.

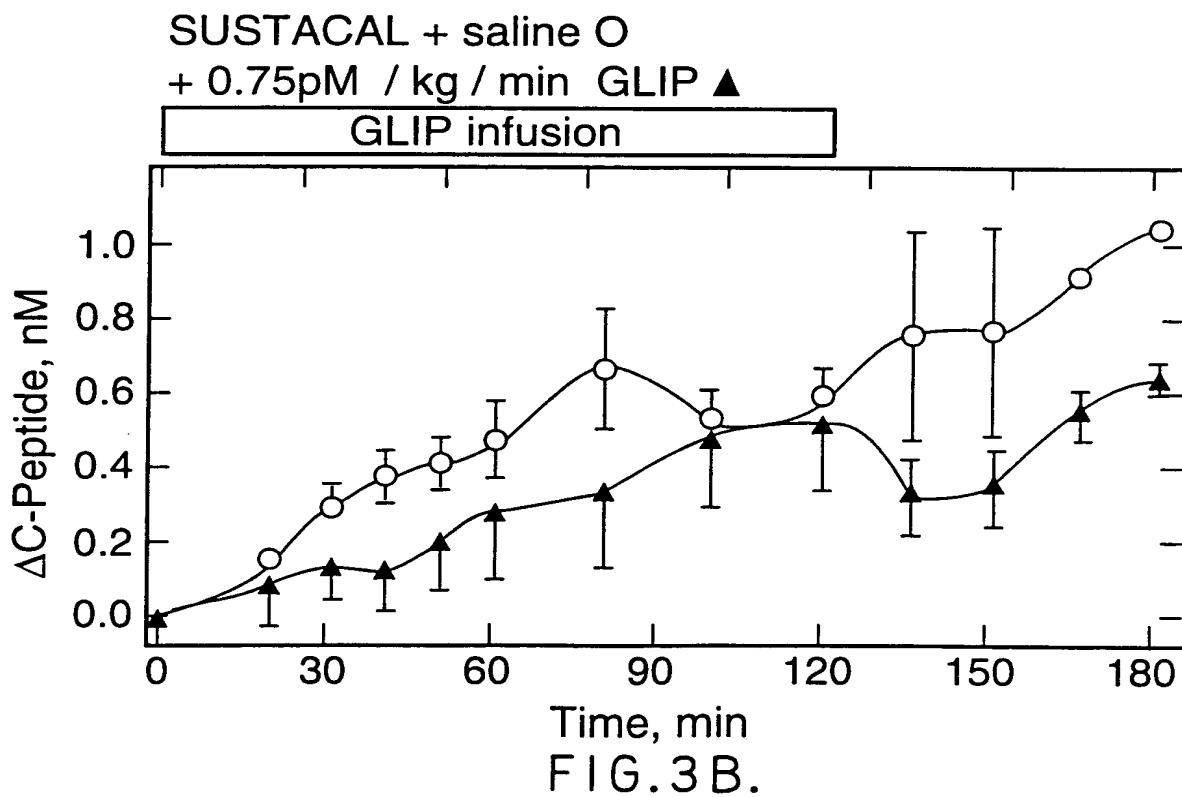
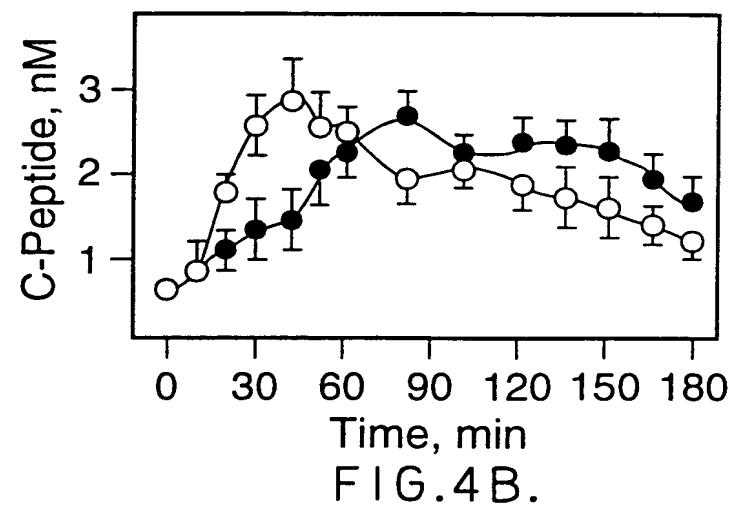
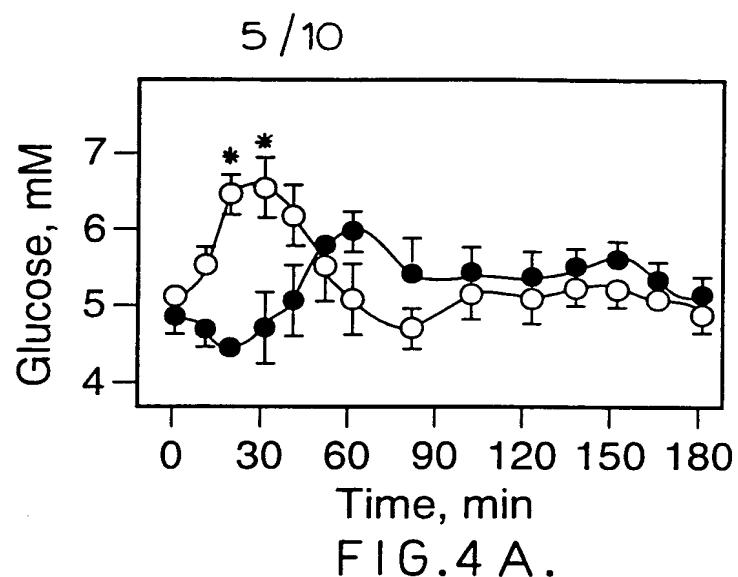
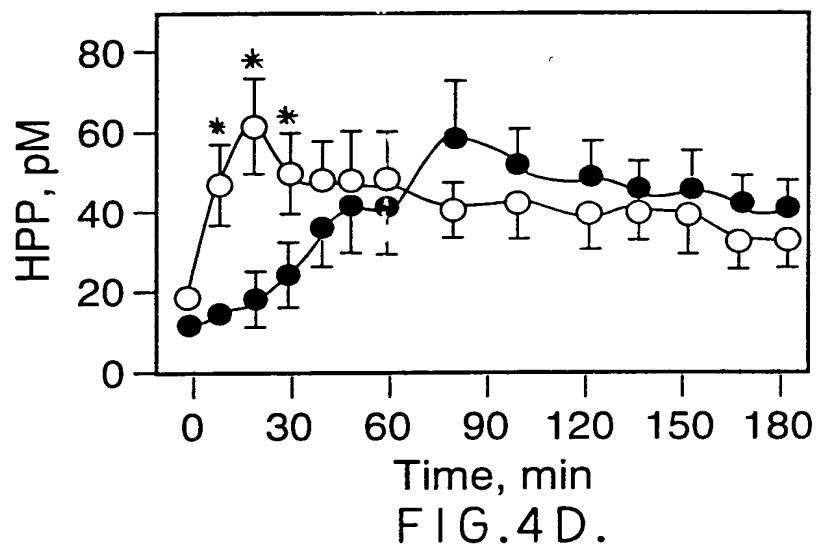
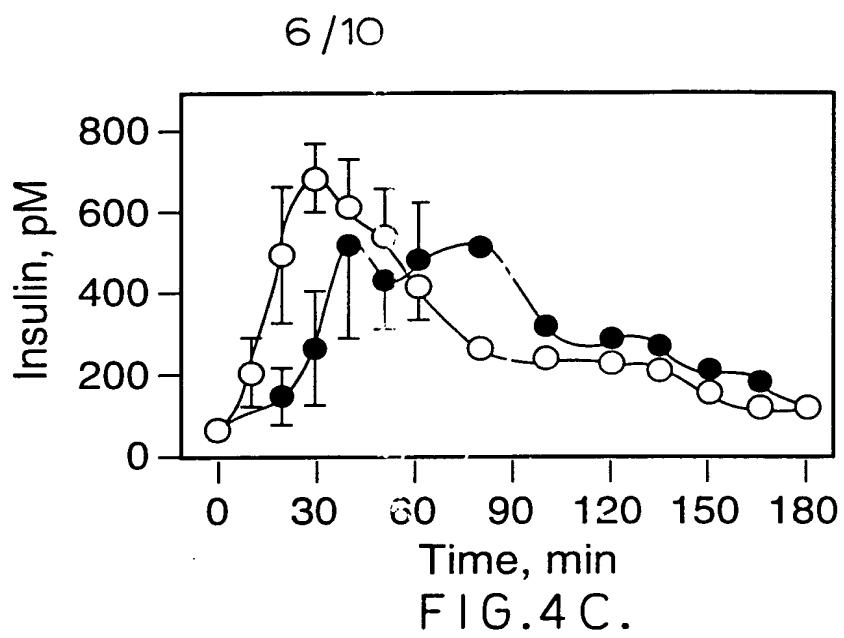


FIG. 3 B.





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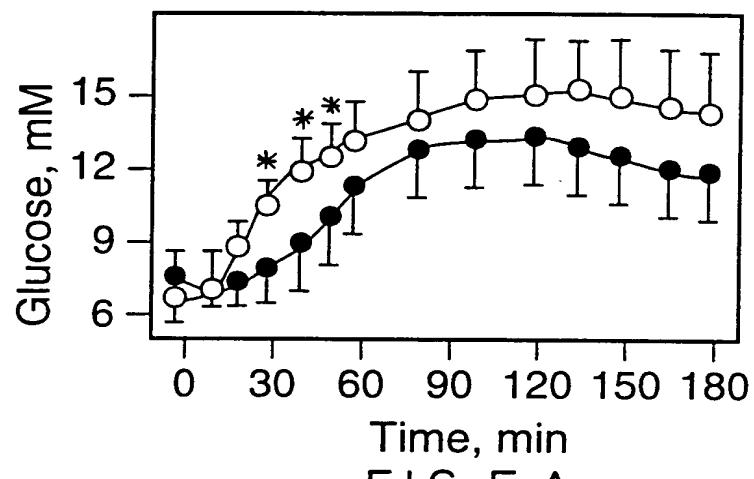


FIG.5 A.

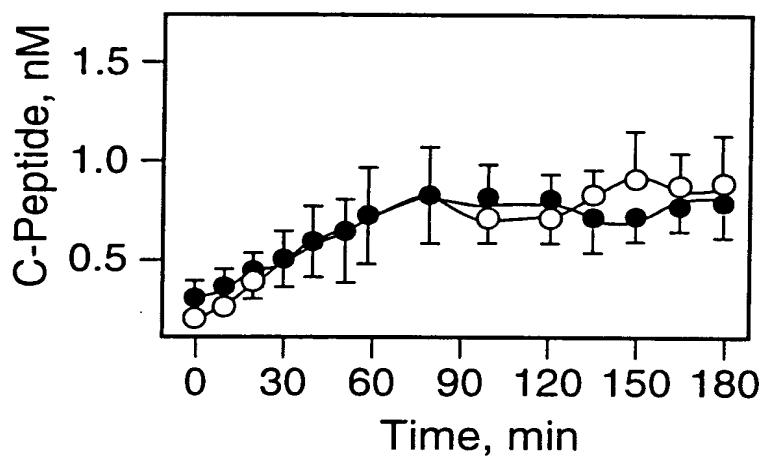


FIG.5 B.

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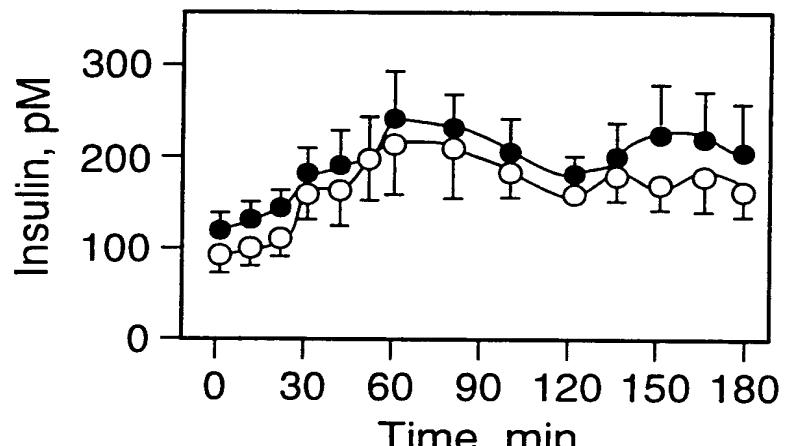


FIG. 5 C.

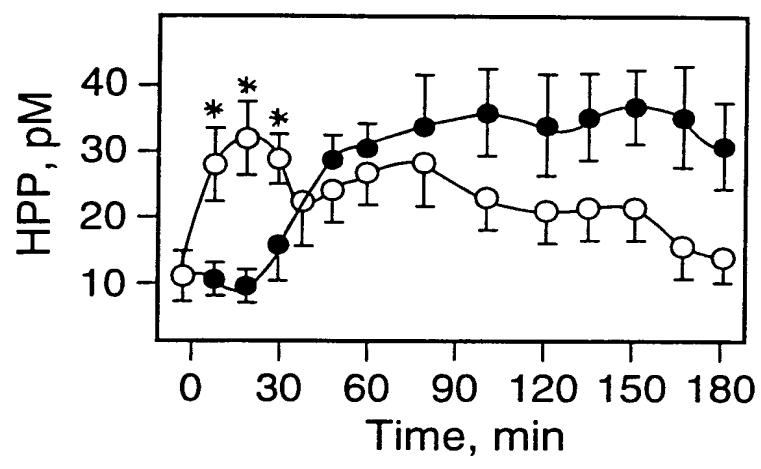


FIG. 5 D.

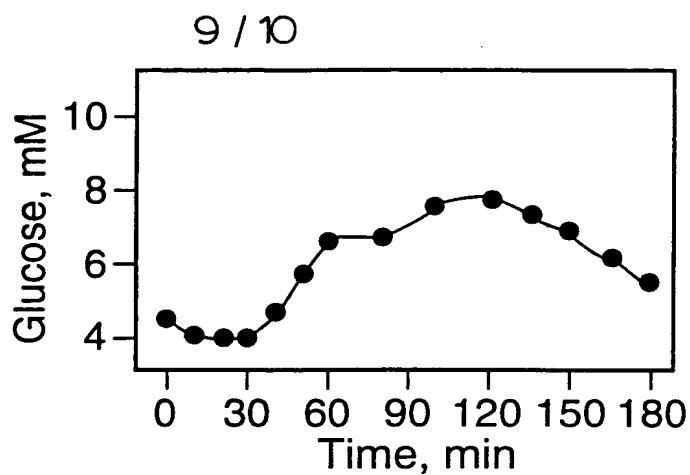


FIG. 6 A.

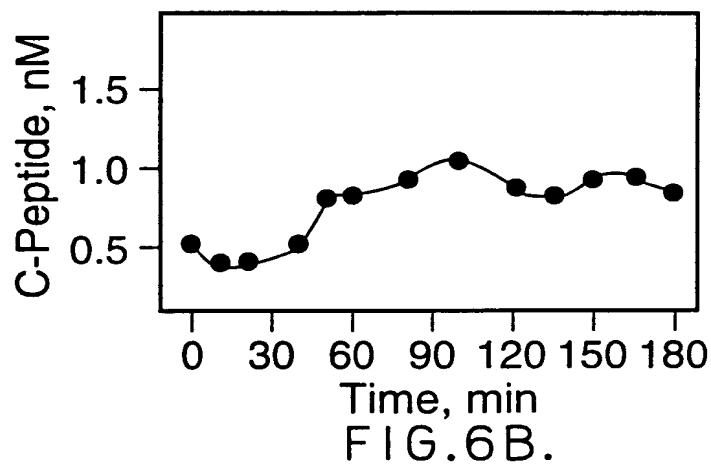


FIG. 6 B.

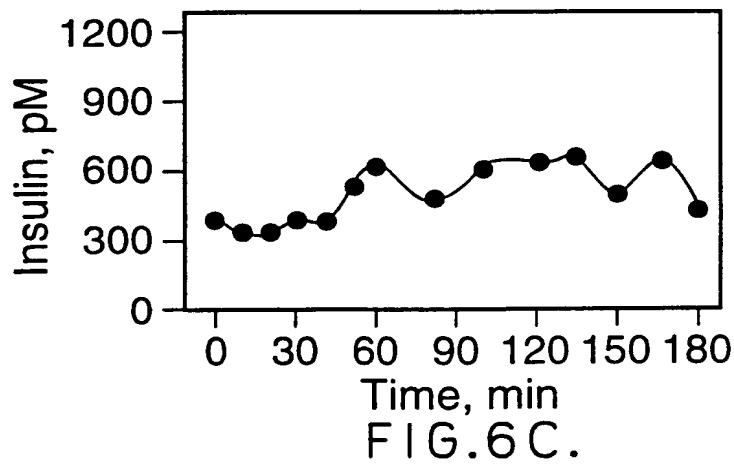
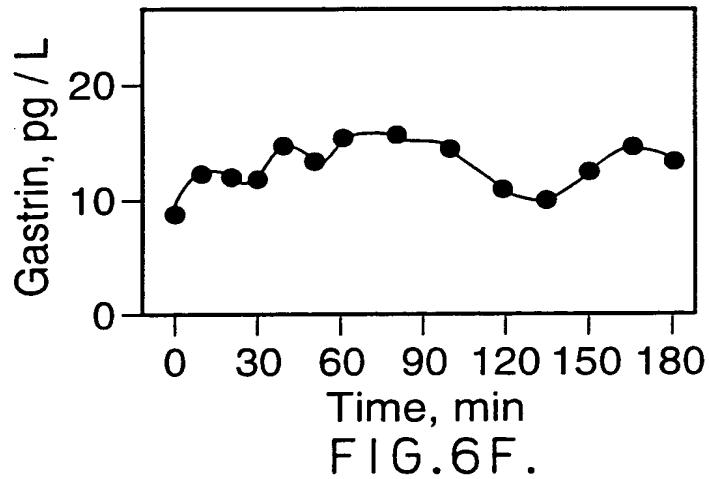
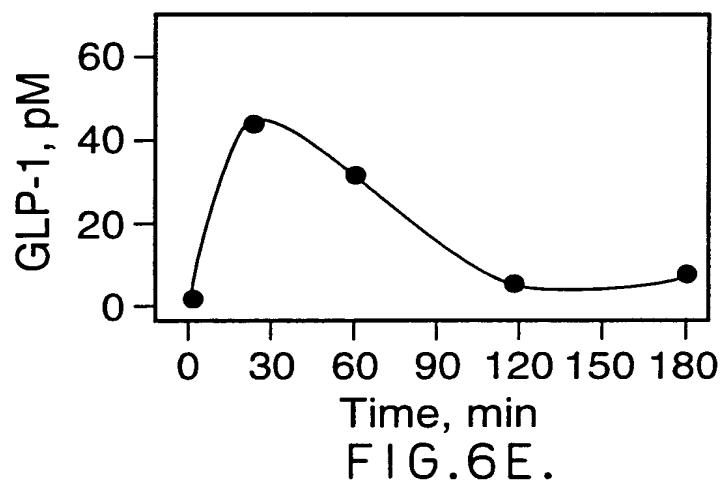
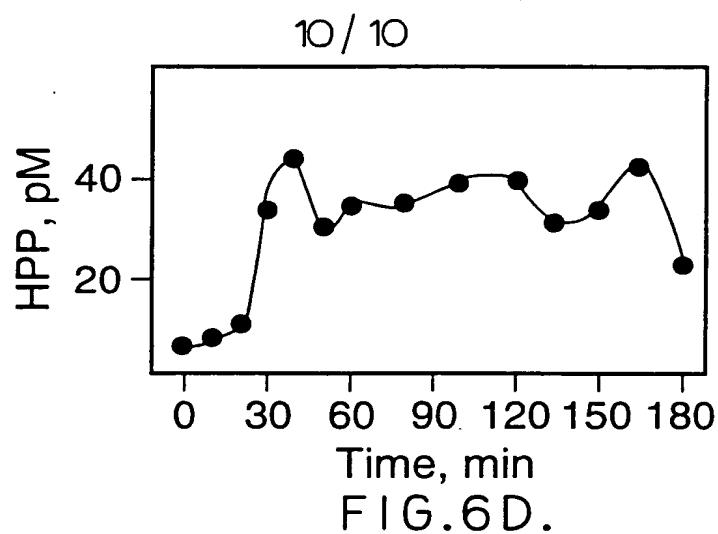


FIG. 6 C.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 95/00287

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K38/26 // (A61K38/26, 38:28)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-91 11457 (BUCKLEY D. ET AL.) 8 August 1991 see the whole document ---	1,5,6
X	THE JOURNAL OF CLINICAL INVESTIGATION, vol. 93, no. 5, May 1994 pages 2263-2266, D'ALESIO D.A. ET AL. 'Glucagon-like Peptide 1 Enhances Glucose Tolerance Both by Stimulation of Insulin Release and by Increasing Insulin-independent Glucose Disposal' see the whole document ---	1-14 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

24 July 1995

Date of mailing of the international search report

07.08.95

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 95/00287

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE NEW ENGLAND JOURNAL OF MEDICINE , vol. 326, no. 20, 14 May 1992 BOSTON (US), pages 1316-1322, GUTNIAK M. ET AL. 'Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus' cited in the application see the whole document ---	1-14
A	WO-A-93 25579 (PFIZER INC.) 23 December 1993 see the whole document -----	1-14

INTERNATIONAL SEARCH REPORT

national application No.

PCT/CA95/00287

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-5, 13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-5, 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 95/00287

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9111457	08-08-91	EP-A-	0512042	11-11-92
WO-A-9325579	23-12-93	AU-B- CA-A- CN-A- EP-A- HU-A- JP-T- NO-A-	4027593 2138161 1085913 0646128 64367 7504679 944853	04-01-94 23-12-93 27-04-94 05-04-95 28-12-93 25-05-95 14-12-94



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No.	Doccode	Number of pages
1	M905	2

Total number of pages: 2

Remarks:

Order of re-scan issued on